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Advances in Temporal Lobe Epilepsy Research

Dr. Wilner:
Temporal lobe epilepsy is a common form of epilepsy in adults that originates in the medial or lateral temporal lobe. It can cause a wide variety of seizures that may be difficult to control with anti-seizure medications. Temporal lobe epilepsy may also be associated with memory loss and psychiatric symptoms and can severely impact a patient's quality of life.

Welcome to *NeuroFrontiers* on ReachMD. I'm your host, Dr. Andrew Wilner. I'm joined by Dr. Sanjay Kumar to help us better understand the pathophysiology underlying temporal lobe epilepsy. Dr. Kumar is a Professor of Biomedical Sciences, Florida State University College of Medicine.

Dr. Kumar, welcome to the program.

Dr. Kumar:
Thank you for having me on this show, Dr. Wilner. I appreciate it very much.

Dr. Wilner:
All right. Well, let's dive right in. Why is it important to study temporal lobe epilepsy?

Dr. Kumar:
Like you very nicely prefaced in your introduction, temporal lobe epilepsy is the most common type of epilepsy in adults and, as you said, the condition that is characterized by recurrent, unprovoked seizures originating from the medial or temporal lobe. Seizures associated with TLE can be simple partial seizures that entail no loss of awareness or complex partial seizures that involve a loss of awareness. The challenge with TLE is refractory to anti-epileptic medications. The pathology, although it's known, is not well-characterized, and the pathophysiology is partially known or unknown, and the cure at this point in time is unavailable. So with about 50 million or so cases of TLE worldwide, this is a serious disease.

Dr. Wilner:
So do we know what's special about temporal lobe epilepsy that makes it so difficult to control, or is that still a mystery too?

Dr. Kumar:
It has remained a mystery for a long time, but we are slowly cracking the mystery, if you will. The reason why temporal lobe epilepsy has been difficult to treat is that we don't have a good handle on the pathology and the pathophysiology. So one example is that we fail to realize that TLE is a neurodegenerative disorder. Cells are lost in very stereotypic ways in different regions of the brain, and cells and circuits are disrupted. From the time of initial precipitating injury to your first seizure, there is a massive disruption in the cells and circuits, so we don't quite know why cells die in these regions in these stereotypic patterns. And I guess that is in my opinion one of the underlying causes for us to not be able to get to the cure, per se, and so this is the reason why drugs are sometimes ineffective in treating this disorder.

Dr. Wilner:
Now you have a recent publication in the *Journal of Neurophysiology.* So tell us what you found.

Dr. Kumar:
Back in 2020, we published a preceding paper to the one that got published in *Journal of Neurophysiology* that allowed us to highlight how we should approach this disease from the perspective of rescuing those neurons or from the perspective of understanding why these neurons die in stereotypic ways in different regions of the brain, and we had concluded that if we block a receptor in the brain called the N-methyl-D-aspartate receptor with a particular antagonist, then we would be able to prevent excitotoxicity and prevent that cell loss. This was a paper that was published in *Nature Communications*. And so that allowed us to hypothesize the expression of this particular receptor, which is five times more calcium permeable than the conventional NMDA receptor. And so we hypothesized that the expression of this particular receptor, this highly calcium-permeable receptor, in specific regions of the brain causes the zones of vulnerability for neurodegeneration. To follow up on that study, we actually in this current study that was published recently in the *Journal of Neurophysiology* tested that hypothesis whether that particular new receptor expressed in these regions where cell loss occurs is responsible for the cell loss, and with this new technique that we developed called area specific tissue analysis, we were able to confirm that a particular subunit of that NMDA receptor was very tightly correlated with cell loss. So in the 2020 study, we were able to block this receptor with a known antagonist, and that not only prevented epileptogenesis, but it also prevented cell loss, so we're very happy to have confirmed this through this study as well.

Dr. Wilner:
All right. So the NMDA receptor, there is a subtype that allows more calcium in?And that's bad?

Dr. Kumar:
That's bad. So the NMDA receptor is a heterotetrametric comprised of four subunits, and this particular subunit which was recently discovered a decade or more ago, called the GluN3 subunit, makes this receptor 5 times more selective to calcium. Calcium, as you know, is a divalent cation, and the more calcium you have causes greater amount of excitability, which is the hallmark of epilepsy, hyperexcitability, and hypersynchrony, so it can cause hyperexcitability, but lots of calcium coming into the cell without being chelated can cause excitotoxicity and cell death. So this particular receptor, that has this particular subunit called the GluN3, we believe we hypothesized to be the underlying reason why neurons expressing this NMDA receptor bring a lot of calcium, and during that hyperexcitability phase, during the seizure, lots of calcium come in, lots of neurons die, and there's a lot of circuit disruption and neurodegeneration as a result of this excessive amount of calcium coming into cells.

Dr. Wilner:
Now is this a receptor for glutamate?

Dr. Kumar:
That is correct. The NMDA receptor is part of underlying learning and memory. It's a very well-studied receptor in the hippocampus in the context of learning and memory, but is also something that we have recently appreciated, and underlying excitotoxicity in cells and cell death, so we studied how it's involved in bringing about pathogenesis.

Dr. Wilner:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and I'm speaking with Dr. Sanjay Kumar about his research helping us to understand the pathophysiology of temporal lobe epilepsy.

Okay, Dr. Kumar, so you've identified a different receptor, right, that's more susceptible to glutamate actions, bringing calcium into the cell, which can result in cell death. Now suppose I say, let's make a drug that we could sell that's going to stop epilepsy." Could you do it?

Dr. Kumar:
That's a very exciting, question, Andrew, and one that we are pursuing quite actively. This compound that blocks this receptor is already known to us. It's D-serine, and the appeal of D-serine as opposed to many other anti-epileptic drugs is that D-serine is very well tolerated in the brain because it's made in the brain, so we are really excited about the fact that we have identified a compound that can prevent excitotoxicity and cell death in the context of temporal lobe epilepsy.

The question remains: how do we get this drug to those specific regions of the brain? And we need to, of course, validate our studies and our findings in the human. The bridge between bench to bedside is quite a large one, and so I'd love to see this work that is being done in the lab here translate into the human condition. And we are very excited, and we are actively involved in trying to address those questions that you raise.

Dr. Wilner:
That's great. Now you've identified this abnormality, but there's always this question. Is it a chicken and an egg? Is this abnormality the result of years and years of seizures, or is it actually the cause of seizures? Any thoughts on that?

Dr. Kumar:
Oh, yeah. We defined initial precipitating injury as something like traumatic brain injury, for example, or a fall or a concussion causes some sort of pathology, loss of neurons, increased inflammation in these zones of vulnerability, and so we believe that it begins with that initial precipitating injury in these regions, and then it goes on progressively during the latent period. After the IPI, the initial precipitating injury, there's a latent period during which the brain is constantly changing. If it is not checked in a proper way, it can then reach a threshold, and you start seeing the phenotype, which is your seizure. So we believe it's the pathology, in this case, the neuroinflammation, that actually brings about seizures. And then once you have seizures and once the seizures are not controlled, then that exasperates the whole situation and the vicious cycle begins.

Dr. Wilner:
Well, I'm very pleased, and I know my patients are that somebody like you is working so hard to make some progress, so we hope that yours and other research efforts will help lead to some new treatments for our patients with temporal lobe epilepsy.Dr. Sanjay Kumar, thank you very much for a great discussion.

Dr. Kumar:
Thank you so much.

Dr. Wilner:
For ReachMD, I'm Dr. Andrew Wilner. To access this and other episodes in our series, visit ReachMD.com/NeuroFrontiers, where you can Be Part of the Knowledge. Thanks for listening.